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SHORT COMMUNICATION

Remifentanil, Fentanyl, or the Combination in Surgical Procedures in the United States: Predictors of Use in Patients with Organ Impairment or Obesity

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Abstract

Introduction Remifentanil has a rapid onset and short duration of action, predictable pharmacokinetic/pharmacodynamic profile, and unlike fentanyl, does not accumulate with repeated or prolonged administration. This study evaluated predictors of remifentanil use in surgical patients with renal or hepatic impairment, or obesity in the United States who received remifentanil, fentanyl, or the combination.

Methods Data (2010) from the US Healthcare National Inpatient Database, State Inpatient Database, State Ambulatory Surgery Database, and private hospital and Medicaid databases were used in this analysis. Patients included had presence of hepatic or renal disease, and/or obesity and were >5 and ≤80 years of age.

Results In 2010, 9,274 patients with renal impairment, 1,896 with hepatic impairment, and 6,278 with obesity were identified. The percentage of surgical patients diagnosed with renal disease, hepatic disease, or obesity who received remifentanil was 41, 28, and 35 %, respectively; 29, 17, and 22 % received both remifentanil and fentanyl, and 30, 55, and 43 % received fentanyl alone, respectively. In patients with renal or hepatic disease the probability of remifentanil use was greater for persons aged >50 years, with Medicare as primary payer, or who were diagnosed with obesity ($p < 0.05$ all comparisons). In obese patients, the probability of remifentanil use was greater for persons aged >50 years or female (both $p < 0.05$). For all 3 disease states, the probability of remifentanil use was lower for those receiving epidural anesthesia or with Medicaid as primary payer ($p < 0.05$ all comparisons).

Conclusion Remifentanil in combination with fentanyl is used less than fentanyl in surgical patients with hepatic impairment or obesity. This is inconsistent with the fact that the pharmacokinetic/pharmacodynamic features of remifentanil suggest it is the preferred intraoperative opioid in these patients. Predictors of remifentanil use in patients with renal or hepatic impairment, or obesity include older age, obesity, and Medicare as primary payer. Remifentanil in combination with fentanyl was significantly less utilized than fentanyl in persons with Medicaid as primary payer even though there was a disproportionate enrollment of beneficiaries with renal or hepatic disease, or obesity in state Medicaid programs.

Key Points

The pharmacokinetic/pharmacodynamic features of remifentanil would suggest that it is the preferred intraoperative opioid versus fentanyl in patients with renal impairment, hepatic impairment, or obesity; however, remifentanil alone or in combination with fentanyl is, in general, used less frequently than fentanyl.

Predictors of remifentanil use in patients with renal impairment, hepatic impairment, or obesity include older age, obesity, and Medicare as primary payer.

Remifentanil in combination with fentanyl was used significantly less than fentanyl in surgical patients with Medicaid as primary payer even though there was a disproportionate enrollment of beneficiaries with renal or hepatic disease, or obesity in state Medicaid programs.

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1 Introduction

Remifentanil is a 4-anilidopiperidine μ-opioid analgesic approved for use as an analgesic agent during induction and maintenance of general anesthesia [1, 2]. It is a fentanyl derivative and its pharmacodynamic effects are, in general, similar to fentanyl and the other fentanyl cogeners [1, 3, 4]. However, the pharmacokinetic profile of remifentanil is unique [1–4]. Its metabolism is independent of the liver and kidneys, unlike other opioids, and it is rapidly eliminated via blood and tissue nonspecific esterases [1, 2]. The primary metabolic pathway is de-esterification of remifentanil to remifentanil acid, a relatively inactive carboxylic acid metabolite with 300- to 4,600-fold less potency than the parent compound [1]. Almost 90 % of the drug recovered in urine is remifentanil acid [1]. Remifentanil is not metabolized by plasma cholinesterase (pseudocholinesterase) and is not appreciably metabolized by the liver or lung [2]. Remifentanil is rapidly absorbed and distributed throughout the body with a mean volume of distribution at steady state of 350 mL/kg and a clearance of approximately 40 mL/min/kg [2].

Remifentanil is considered a true short-acting opioid, with a rapid onset of action of approximately 1 min [1, 3] and a short offset of action of approximately 5–10 min [2]. Its offset of action is not affected by duration of drug infusion, and remifentanil does not accumulate with repeated and prolonged administration, unlike other opioids [5, 6]. The context-sensitive half-time of remifentanil is approximately 3–4 min irrespective of infusion duration [3, 5, 6].

These features of remifentanil would be of benefit to certain populations of patients, especially at-risk patients where drug clearance may be substantially reduced due to illness, organ dysfunction, or concomitant therapy. The pharmacokinetics of remifentanil are not affected in any clinically significant way in several at-risk patient groups. No differences are seen in the pharmacokinetic profile of patients with or without renal impairment, or in patients with end-stage renal disease [7, 8]. The pharmacokinetics of remifentanil and its major metabolite, remifentanil acid, are unchanged in patients with severe hepatic impairment [9, 10]. In obese patients, when dosing is adjusted to ideal body weight, no differences in pharmacokinetics are observed between obese and lean patients [11].

Remifentanil has been shown to be an effective and safe analgesic component in the anesthetic management of patients with renal impairment [12], hepatic impairment [13], and obesity [14–17]. For these patients, where rapid titration and precise control of analgesia in response to hemodynamic fluctuations is essential [18–20], as well as rapid and predictable emergence from anesthesia regardless of duration of anesthesia, remifentanil may be better suited than fentanyl as an adjunct in their general anesthesia requirements.

Fentanyl is widely distributed in the body, with a volume of distribution at steady state of 4 L/kg [21]. It is extensively metabolized by the liver with a high hepatic clearance (approaching that of hepatic blood flow) and a high hepatic extraction ratio (0.8–1.0) [21]. Unlike remifentanil, the context-sensitive half-time of fentanyl is dependent on infusion duration, with accumulation and prolongation of effect increasing as infusion time increases [6]. The time required for a 50 % reduction in the effect-site concentration of fentanyl is over 65 times greater than that of remifentanil [6].

The following study evaluated predictors of remifentanil use, fentanyl use, or the combination of the two drugs in surgical patients with renal impairment, hepatic impairment, and/or obesity in the United States.

2 Methods

2.1 Data Source

This study evaluated administrative claims data (January 1, 2010, to December 31, 2010) from the US Healthcare Cost and Utilization Project's National Inpatient Database, State Inpatient Database, and State Ambulatory Surgery Database (US Department of Health and Human Services, Agency for Healthcare Research and Quality) [22] and from MarketScan® Hospital Drug Database and MarketScan® State Medicaid Database.

2.2 Study Population

Patients aged >5 and ≤80 years with renal impairment, hepatic impairment, and/or obesity were identified by international classification of disease (ICD-9-CM) codes: 584.x-585.x (renal impairment), 570.x-573.x (hepatic impairment), and 278.x (body mass index >30 kg/m^2 for obesity) from 8 categories of surgical procedures identified by ICD-9-CM and/or current procedure terminology codes: cardiac, general, gynecology, orthopedic, otolaryngology, neurology, thoracic, and vascular [23]. Patients were included in the study if they received remifentanil hydrochloride, fentanyl, or a combination of remifentanil HCL and fentanyl for surgical procedures. Patients were excluded if they were transferred to another facility.

2.3 Assessments

Baseline characteristics and other factors that may be predictive of patients receiving remifentanil, fentanyl, or

the combination of these two drugs were evaluated including age, sex, disease state (renal impairment, hepatic impairment, obesity), comorbidities (identified by ICD-9-CM codes), healthcare plan (Medicaid, Medicare, or private), use of epidural drugs, and facility characteristics (hospital or outpatient; bed size, location [urban; rural]; ownership).

2.4 Statistical Analysis

Hierarchical mixed-effects logistic regression analysis was used to discern factors predictive of receipt of remifentanil, fentanyl, or the combination in patients with renal impairment, hepatic impairment, and/or obesity. The a priori significance level was $p < 0.05$. Odds ratio (OR) and 95 % confidence intervals (CI) were adjusted for patient-level Charlson/Deyo score (index for predicting mortality by comorbid conditions) and facility characteristics (public/private, teaching/nonteaching, urban/rural). Analysis was conducted using SAS® (version 9.1.3; SAS Research Institute, Cary, NC, USA), and STATA® (version 12; STATA Corporation, LP, College Station, TX, USA). Data on percentage of patients receiving remifentanil, fentanyl, or the combination are presented using descriptive statistics only.

3 Results

A total of 9,274 patients were identified in 2010 with renal impairment, 1,896 with hepatic impairment, and 6,278 with obesity (Table 1). There were slightly more male than female patients in each of the disease groups, and the mean age of patients was highest in the renal-impairment patients and lowest in the obese patients.

Of the patients identified with renal impairment, 41 % received remifentanil, 29 % received a combination of remifentanil and fentanyl, and 30 % received fentanyl alone (Fig. 1). Twenty-eight percent of the patients identified with hepatic impairment received remifentanil, while 17 % received the combination of the two drugs and 55 % received fentanyl alone. Among the obese patients, 35, 22, and 43 % received remifentanil, a combination of remifentanil and fentanyl, or fentanyl alone, respectively.

3.1 Predictors of Remifentanil Use in Surgical Patients with Renal Impairment, Hepatic Impairment, or Obesity

In patients with renal impairment or hepatic impairment, the probability of remifentanil or combination remifentanil and fentanyl use versus fentanyl alone was significantly greater for patients aged >50 years, diagnosed with obesity, or having Medicare as their primary payer (relative to private payer) (Table 2). The probability of remifentanil or combination remifentanil and fentanyl use versus fentanyl in both groups of patients was significantly lower for those receiving epidural anesthesia and for those having Medicaid as the primary payer.

The probability of remifentanil or combination remifentanil and fentanyl use versus fentanyl alone was significantly greater for obese patients that were female and aged >50 years, (Table 2) and significantly lower for obese patients receiving epidural anesthesia or having Medicaid as their primary payer.

4 Discussion

The results of this study found that remifentanil, with or without fentanyl, was used in 70 % of the surgical patients with renal impairment, 45 % of those with hepatic impairment, and 57 % of those with obesity. The numbers for patients with hepatic impairment or obesity were lower than expected. In severe liver failure patients, single bolus or low-dose fentanyl can be used; however, accumulation of fentanyl is a concern with repeated or high doses [24]. The metabolism of remifentanil is unchanged in severe liver disease patients as metabolism is via tissue and blood esterases, making it an attractive opioid component of the anesthetic regimen for patients with hepatic impairment [24].

Obesity was found to be a positive predictor of remifentanil use. Obesity is associated with a number of comorbid conditions that affect the administration of anesthesia including restrictive lung disease, obstructive sleep apnea, diabetes, hypertension, pulmonary hypertension, cardiomegaly, liver disease, and delayed gastric emptying [25, 26]. Obese patients also have a higher prevalence of cardiovascular disease, including hypertension, arrhythmias, stroke, heart failure, and coronary artery disease [26], which can contribute to difficulties in maintaining a stable circulatory status in these patients. Airway procedures may be more difficult in these patients and they may have more difficulty breathing during anesthesia [26]. Operating time may be longer in an obese patient due to technical challenges faced by the surgeon when the anatomy is distorted or hidden behind excessive fat. The longer exposure to general anesthesia may cause delayed awakening of the patient or lead to over-sedation and subsequent postoperative complications, including respiratory depression [18]. Use of remifentanil has been shown to result in shorter extubation times, earlier mobilization of patients, and potential minimization of postoperative complications such as respiratory depression or hypoxemia [15, 18, 19].

Table 1 Patient demographics and baseline characteristics

Variable	Renal disease[a] (n = 9,274)	Hepatic disease[a] (n = 1,896)	Obesity[a] (n = 6,278)
Age (years)			
Mean ±SD	53.5 ± 13.5	49.2 ± 17.8	39.4 ± 15.7
Median	53.0	48.0	37.0
Range	32–74	21–80	16–74
Sex (%)			
Male	58	64	53
Payer (%)			
Medicaid	76	63	51
Medicare	17	19	22
Private	7	18	27
Epidural anesthesia			
Yes (%)	31	28	29
Obesity (278.x)[a]			
Yes (%)	24	17	–

[a] Categorized by ICD-9-CM codes: 570.x-573.x for hepatic disease, 584.x-585.x for renal disease, 278.x (body mass index >30 kg/m^2) for obesity

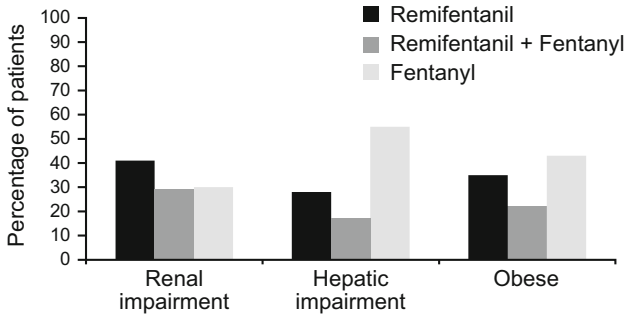

Fig. 1 Percentage of renal-impaired, hepatic-impaired, or obese patients receiving remifentanil, fentanyl, or a combination of remifentanil and fentanyl

These features are also important for patients with organ impairment, many of whom are advanced in age. Elderly patients have reduced organ functional reserves and reduced compensatory mechanisms in response to stress, and medications are cleared from the body at a slower rate [25, 27]. There is an increased risk for postoperative complications in the elderly that includes adverse drug reactions, postoperative cognitive dysfunction, and delirium [25, 27]. Use of drugs associated with delirium in the elderly such as long-acting opioids, benzodiazepines and anticholinergics should be limited [25]. It is important that the anesthetic regimen used for elderly patients provides intraoperative stability combined with rapid emergence to minimize the incidence of postoperative cognitive impairment and side effects [27]. Recovery time with remifentanil-nitrous oxide anesthesia has been shown to be shorter than with fentanyl-isoflurane-nitrous oxide anesthesia in a study of elderly patients aged 65 years and older undergoing spinal surgery [28]. Patients receiving the remifentanil-based regimen had shorter time to eye opening, extubation, and spontaneous respiration versus the fentanyl-based regimen [28]. Such results support the finding from this study that older age (>50 years) is a predictor of remifentanil use.

Remifentanil, alone or in combination with fentanyl, was used significantly less than fentanyl in patients for whom the primary payer was Medicaid, even though there was a disproportionate enrollment of beneficiaries with renal or hepatic disease and/or obesity in state Medicaid programs. These payor results would suggest that access to remifentanil may be an issue for low-income patients. Perceived differences in cost for remifentanil versus fentanyl may be a barrier to remifentanil use. The drug cost of remifentanil is higher than that of fentanyl; however, drug costs are only a small part of total healthcare costs [20]. Synergistic effects of anesthetic drugs and use of concomitant drugs all affect total costs. In addition, differences in time the patient is in surgery and differences in recovery and postoperative side effects all affect hospital, surgical, and postoperative expenditures.

Unfortunately, hardly any studies published in the United States evaluate in a comprehensive manner overall hospital or all anesthesia-related cost comparisons between remifentanil and fentanyl. The few existing American studies that analyze other costs in addition to opioid drug costs do suggest that when other costs are taken into account, such as total hospital costs or total anesthesia-related drug costs, the two drugs are comparable [29–31].

Engoren et al. [30] evaluated the cost of fast-track cardiac surgery in 90 adult patients who received remifentanil-based, sufentanil-based, or fentanyl-based anesthesia. The investigators found that although the median opioid and anesthetic costs of remifentanil were higher than those of fentanyl, total hospital cost (sum of direct variable cost for

Table 2 Patient characteristics predictive of remifentanil or combination of remifentanil and fentanyl use versus fentanyl alone in renal-impaired, hepatic-impaired, and obese patients

Characteristic	OR and 95 % CI[a]		
	Renal disease ($n = 9,274$)	Hepatic disease ($n = 1,896$)	Obesity BMI > 30 ($n = 6,278$)
Age, years			
0 = <50	1.37 (1.13–1.58)*	1.21 (1.08–1.46)*	1.49 (1.28–1.62)*
1 = ≥50			
Sex			
1 = Women	1.05 (0.93–1.12)	0.92 (0.85–1.13)	1.23 (1.07–1.45)*
0 = Men			
Payer			
Medicaid	0.78 (0.51–0.88)*	0.85 (0.63–0.91)*	0.81 (0.64–0.93)*
Medicare	1.94 (1.56–2.33)*	1.69 (1.37–1.85)*	0.93 (0.78–1.06)
Private (reference)[b]			
Epidural anesthesia			
1 = Yes	0.42 (0.27–0.61)*	0.64 (0.52–0.79)*	0.75 (0.61–0.83)*
0 = No			
Obesity			
1 = Yes	1.19 (1.07–1.35)*	1.36 (1.18–1.63)*	N/A
0 = No			

BMI body mass index, *CI* confidence interval, *OR* odds ratio

* $p < 0.05$

[a] Adjusted for patient-level Charlson/Deyo score (index for predicting mortality by comorbid conditions); facility characteristics (public/private; teaching/nonteaching; urban/rural)

[b] OR and 95 % CI relative to private payer (e.g., managed care; health maintenance organization)

each item and service used by the patient from preoperative period through to discharge or death) was comparable between the two groups. No significant differences were found in median ventilator times, intensive care unit (ICU) stays, and hospital stays between the anesthesia regimens.

Reddy et al. [31] evaluated the cost of coronary artery bypass graft surgery with remifentanil-based anesthesia versus fentanyl-based anesthesia in 59 adult patients. Anesthetic costs were higher for remifentanil versus fentanyl; however, pulmonary function testing costs, recovery room costs, and ward costs were lower with remifentanil than with fentanyl. Length of stay and other costs such as medical and surgical supplies, operating room, ICU, laboratory, radiology, pharmacy, and transfusion costs were similar between the two treatments. Taken together, the total costs of remifentanil and fentanyl were comparable.

A retrospective cost analysis of a controlled multicenter clinical study evaluating patients ($N = 63$) undergoing craniotomy found that total anesthesia drug-related costs were less with remifentanil than with fentanyl for all price considerations except at the lowest average wholesale price (AWP) of fentanyl [29]. Total drug costs were based on a range of AWPs for the two opioids as well as all concomitant drugs used in the intraoperative and immediate postoperative periods that were related to the choice of opioid during surgery.

For certain short duration surgeries, anesthetic costs alone may be comparable between remifentanil and fentanyl. In a study by Jellish et al. [32], the anesthetic cost of remifentanil-based total intravenous anesthesia (TIVA) anesthesia supplemented with low-dose propofol in patients undergoing otologic procedures (1–2 h procedures) was $\$69 \pm 7$ versus $\$66 \pm 5$ for propofol-based TIVA with supplemental fentanyl. Patients receiving the remifentanil-based anesthesia had better hemodynamic stability, less movement, and faster emergence from surgery. Postoperative pain scores were mild for both groups, but higher in the remifentanil group. All other variables examined were similar, including incidence and severity of postoperative nausea and vomiting, mean time to hospital discharge, ambulation without dizziness and other recovery parameters, and patient satisfaction with anesthesia.

More studies are needed that evaluate aggregate costs of pharmacotherapy with remifentanil versus fentanyl, not only in higher-risk patients such as those with renal and hepatic impairment and obese patients, but also in certain surgeries where the pharmacokinetic benefits of remifentanil over other opioids may prove advantageous.

A limitation of this study is the retrospective nature of the analysis. ICD-9-codes were used to identify patients with renal impairment, including those with acute renal failure. There is no differentiation between presurgical or postsurgical occurrence of acute renal failure. It is possible that some of the patients included in this analysis had this condition as a consequence of surgery. Due to the fast offset of effect of remifentanil, another analgesic is required prior to discontinuation of remifentanil general anesthesia if postoperative pain is anticipated and remifentanil infusion is not continued into the postoperative period. Fentanyl may have been used for postoperative pain

and may be included in the fentanyl plus remifentanil group; however, no separate evaluation of this parameter was conducted.

5 Conclusion

The type of analgesic pharmacotherapy should be predicated on the clinical presentation of a given patient (e.g., hepatic disease, renal disease, obesity) and the pharmacokinetic and metabolic profile of an agent.

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